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Clinical significance and outcomes of *Clostridium perfringens* bacteremia—a 10-year experience at a tertiary care hospital

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SUMMARY

Background: The mortality rate of patients with *Clostridium perfringens* bacteremia is 27–44%. Typically, the clinical characteristics of this infection are non-specific, which leads to considerable difficulty with the diagnosis and early initiation of appropriate therapy.
Methods: A retrospective cohort study of patients who were hospitalized between August 2002 and July 2011 with *C. perfringens* bacteremia was conducted within a 3715-bed teaching hospital in northern Taiwan. The patients identified in this search were included when they had fever or other clinical features suggestive of systemic infection. Multiple logistic regression analysis was applied to determine the independent risk factors of 30-day mortality.
Results: A total of 93 patients were identified. Elderly patients with comorbid illnesses, especially renal insufficiency or malignancy, were at risk of developing *C. perfringens* bacteremia, and 23 patients (24.7%) had nosocomial bacteremia. The 30-day and attributed mortalities were 26.9% (25/93) and 8.6% (8/93), respectively. Nosocomial infection was a significant predictor for mortality within 30 days (odds ratio 19.378, 95% confidence interval 2.12–176.99; $p = 0.009$), independent of other disease parameters. Other independent risk factors included the Charlson weighted index of comorbidity, length of hospitalization, and stay in the intensive care unit.
Conclusions: Early recognition of this critical infection and early initiation of appropriate antibiotic treatment by surgical intervention or drainage is essential.

1. Introduction

Clostridium species are Gram-positive, spore-forming, obligate anaerobic bacilli. Generally, many of them are considered saprophytic, and some are pathogenic to humans and animals.[1,2] Clostridia are ubiquitous and found in soil, decaying vegetation, marine sediment, and the intestinal tract of humans. *Clostridium perfringens*, the most frequent clinical isolate of Clostridium, is often encapsulated, non-motile, and rarely sporulated in artificial media. *C. perfringens* strains are classified into five types, A through E, according to lethal toxin production. *C. perfringens* patients exhibit various clinical symptoms, including infections of skin and soft tissue,[3] gastroenteritis,[4] gas gangrene,[5] necrotizing enteritis,[4] liver abscess,[6] endophthalmitis,[7] bacteremia, and septic shock with acute hemolysis.[5,8–12]

The 30-day mortality rate of patients with *C. perfringens* bacteremia is 27–44%,[5,13–16] and most infections have exhibited no specific clinical characteristics except for minimal systemic inflammatory syndromes. This finding indicates that an early diagnosis and initiation of appropriate treatment for *C. perfringens* bacteremia may be very difficult. Because a limited number of studies have investigated the clinical characteristics and risk factors for mortality among patients with *C. perfringens* bacteremia, we conducted a retrospective cohort study in a large tertiary care hospital. Our aims were to: (1) describe the characteristics of clinically significant *C. perfringens* bacteremia cases in a large tertiary care hospital over a 10-year period; (2) define the risk factors of fatal *C. perfringens* bacteremia relative to non-fatal cases; and (3) determine the differences between community-acquired and nosocomial *C. perfringens* bacteremia.

2. Methods

2.1. Study design and setting

This retrospective cohort study was conducted at the Chang Gung Memorial Hospital at Linkou (CGMH-Linkou), a 3715-bed university-affiliated academic tertiary care medical center in northern Taiwan. The study was approved by the institutional review board of the CGMH-Linkou (Number 100-2949B).

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2.2. Patients and case definition

All inpatients with an episode of *C. perfringens* bacteremia occurring between August 2002 and July 2011 were identified through the Clinical Microbiology Laboratory, which processes all clinical specimens. A case was considered when a patient had at least one blood culture positive for *C. perfringens* during the period of microbial isolation and exhibited clinical features suggestive of a systemic infection. For patients with multiple episodes of *C. perfringens* bacteremia, only the first episode was included in the analysis.

2.3. Microbiological identification and susceptibility testing of C. perfringens isolates

Identification and susceptibility testing of *C. perfringens* were performed and interpreted according to standard methods.[17,18] In addition, culture on kanamycin–vancomycin–colistin–laked blood agar (LBA) plates (BD Microbiology Systems, Cockeysville, MD, USA)[19] was used to differentiate isolates. Antimicrobial susceptibility testing was performed by the agar dilution method described by the Clinical and Laboratory Standards Institute, with the use of Brucella–LBA containing hemin and vitamin K1 (BD Microbiology Systems, Cockeysville, MD, USA).[19] The tested antibiotics in the panel were penicillin, clindamycin, piperacillin, metronidazole, and ampicillin/sulbactam.

2.4. Data collection

Patient medical records were used as the source of data for demographics, comorbid illnesses, coexisting bloodstream pathogens, clinical features, Charlson weighted index of comorbidity (WIC),[20] Pitt bacteremia score,[21] laboratory and imaging findings, sources of bacteremia, length of hospitalization, stay in intensive care unit (ICU), outcomes, and susceptibility tests on blood isolates. The comorbid illnesses that we identified in our patients included renal insufficiency (defined as serum creatinine $\geq$1.4 mg/dl, or the requirement for hemodialysis), malignancy, diabetes mellitus, hypertension, liver cirrhosis, cerebral vascular accident, heart failure, gall stones, bowel obstruction, use of immunosuppressants (defined as the use of prednisone during hospitalization (20 mg per day or equivalent for at least 2 weeks, or 100 mg per day for at least 3 days), or chemotherapy for cancer patients within 14 days of bacteremia onset), and recent surgery (surgical procedures performed 3 months or less before the onset of infection).

Community-acquired bacteremia was defined as a positive blood culture taken within 48 h of admission or true community onset. Nosocomial bacteremia was defined as a positive blood culture obtained more than 48 h after admission. Polymicrobial bacteremia was defined as one or more additional bacterial species isolated from blood concurrently with *C. perfringens*. The Pitt bacteremia score was calculated to assess the severity. Scoring was based on the following criteria: (1) ear temperature, 2 points for $<$35 °C or $\geq$40 °C, 1 point for 35.1–36.0 °C or 39.0–39.9 °C, and 0 points for 36.1–38.9 °C; (2) hypotension, 2 points for acute hypotensive event with $>$30 mmHg decrease in systolic blood pressure and $>$20 mmHg decrease in diastolic pressure, the use of intravenous vasopressor agents, or a systolic pressure $<$90 mmHg; (3) the need for mechanical ventilation, 2 points; (4) cardiac arrest, 4 points; and (5) mental status, 0 points if alert, 1 point if disoriented, 2 points if stuporous, and 4 points if comatose.

The Charlson WIC was determined by the sum of the following assigned scores for each condition: 1 for myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, or diabetes; 2 for hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, tumors (any), leukemia, or lymphoma; 3 for moderate or severe liver disease; and 6 for metastatic solid tumors and AIDS.

Leukocytosis was defined as leukocytes $>10 \times 10^9$ cells/l and leukopenia as leukocytes $<4 \times 10^9$ cells/l. Neutropenia was defined as absolute neutrophils $<0.5 \times 10^9$ cells/l. Anemia was defined as hemoglobin $<$13 g/dl in men and $<$12 g/dl in women. Thrombocytopenia was defined as platelets $<150 \times 10^9$ cells/l. Hepatic dysfunction was defined as the occurrence of two or more of the following: bilirubin concentration $>$2.5 mg/dl, aspartate aminotransferase or alanine aminotransferase $\geq$2 times the upper normal limit, and known severe liver disease. Fever was defined as any body temperature $\geq$38 °C, and hypothermia was defined as any body temperature $<$36 °C.

Sources of bacteremia were determined from the medical records, imaging studies, surgical findings, and microbiological evidence, not only by the physician in charge, but also by the review of an infection specialist. Bacteremia sources were classified as intra-abdominal sites, lower or upper respiratory tract, skin, bone and soft tissue, urinary tract, and primary without any definite focus. Adequate antimicrobial treatment was defined as antibiotics effective against *C. perfringens* in vitro being administered within 48 h of bacteremia onset, subsequent to the receipt of final blood culture results, and continuously for at least 3 days. Adjunctive therapy was defined as concurrent to surgical intervention or palliative drainage.

The 30-day mortality, defined as the mortality within 30 days of bacteremia onset, was recorded. Bacteremia-attributed mortality was considered if mortality occurred within 7 days of *C. perfringens* bacteremia onset, with profound shock, multiple organ failure, and no other identified cause of death.

2.5. Statistical analysis

Categorical variables were compared using the Chi-square test or Fisher's exact test as appropriate. Continuous variables were tested for normality of distributions by the Kolmogorov–Smirnov test and compared by the Student's *t*-test or Mann–Whitney *U*-test as appropriate. The odds ratio (OR) and 95% confidence interval (CI) were calculated as well. In the univariate analysis, variables with a two-tailed $p < 0.05$ were included in a multiple logistic regression to determine independent risk factors for 30-day mortality. All tests were two-tailed, and $p < 0.05$ was considered significant in the multivariate analysis. All statistical calculations were performed with standard programs of the Statistical Package for the Social Sciences for Windows, version 18.0 (PASW, Chicago, IL, USA).

3. Results

3.1. Demographics, comorbidities, and microbiological characteristics

Based on inclusion of the first episode of bacteremia only, 132 patients with *C. perfringens* bacteremia were identified; the overall annual incidence was 0.97 per 100 000 population during the study period. Of these, 39 were excluded from the study for incomplete treatment course (two patients), lack of complete medical records (two patients), and lack of correlated clinical features suggestive of systemic infection (35 patients). Finally, 93 patients were included in the analysis. After exclusion of four patients' isolates that lacked adequate clinical information, 72.7% (93/128) of the clinical blood isolates were clinically significant. The corresponding demographics and clinical features are summarized in Table 1. The mean age of the patients was 70.7 years (range 38–94 years) and males were predominant (54/93 patients, 58.1%). The most common comorbidities were renal insufficiency (49.5%), malignancy (41.9%), and

Table 1
Clinical characteristics of the 93 patients with *Clostridium perfringens* bacteremia

Characteristics	Values[a]
Demographics	
Male gender	54 (58.1%)
Age, years	70.7 ± 13.1
Comorbidities	
Renal insufficiency	46 (49.5%)
Malignancy	39 (41.9%)
Hypertension	24 (25.8%)
Diabetes mellitus	21 (22.6%)
Liver cirrhosis	16 (17.2%)
Cerebral vascular accident	11 (11.8%)
Heart failure	10 (10.8%)
Use of immunosuppressants	10 (10.8%)
Gall stones	6 (6.5%)
Bowel obstruction	2 (2.2%)
Recent admission	19 (20.4%)
Recent surgery	11 (11.8%)
Initial presentations	
Nosocomial infection	23 (24.7%)
Polymicrobial bacteremia	51 (54.8%)
Pitt bacteremia score	2.4 ± 2.98
Charlson WIC	3.6 ± 2.63
Leukocytosis	52 (55.9%)
Leukopenia	10 (10.8%)
Neutropenia	3 (3.2%)
Anemia	57 (61.3%)
Thrombocytopenia	38 (40.9%)
Liver dysfunction	39 (41.9%)
Fever	54 (58.1%)
Abdominal pain	42 (45.2%)
Change of consciousness	15 (16.1%)
Shock at presentation	11 (11.8%)
Weakness	7 (7.5%)
Hypothermia	7 (7.5%)
Gas formation	6 (6.5%)
Sources of bacteremia	
Intra-abdominal[b]	49 (52.7%)
Unknown primary	23 (24.7%)
Lower respiratory tract	18 (19.4%)
Upper respiratory tract	1 (1.1%)
Skin, soft tissue, and bone	1 (1.1%)
Urinary tract	1 (1.1%)
Therapy and outcomes	
Adequate antimicrobial treatment	59 (63.4%)
Surgical treatment	14 (15.1%)
Drainage or aspiration	16 (17.2%)
Stay in ICU	31 (33.3%)
Length of hospital stay, days	23.3 ± 22.8
30-day mortality	25 (26.9%)
Attributed mortality	8 (8.6%)
Antibiotic sensitivity testing[c]	
Clindamycin	90 (96.8%)
Metronidazole	93 (100%)
Penicillin	89 (95.7%)
Piperacillin	93 (100%)
Ampicillin/sulbactam	93 (100%)

WIC, weighted index of comorbidity; ICU, intensive care unit.
[a] Results are *n* (%), or mean ± standard deviation.
[b] Eleven patients had peritonitis, 11 had cholangitis, eight had cholecystitis, seven had liver abscess, four had hollow organ perforation, three had pancreatitis, three had diverticulitis, and one had intra-abdominal abscess and colitis.
[c] Data are antibiotic susceptibility rates of blood isolates of *C. perfringens* from each group, presented as number of isolates (susceptibility rate %).

hypertension (25.8%). Of the malignancies in 39 patients, gastrointestinal (GI) malignancy was the most common ($n = 26$ patients), followed by urogenital ($n = 5$), lung ($n = 3$), sarcoma ($n = 2$), leukemia ($n = 2$), and unknown malignancies ($n = 1$). Of the 26 GI malignancies, hepatocellular carcinoma was the most common ($n = 13$ patients), followed by cholangiocarcinoma ($n = 5$), colorectal ($n = 4$), gastric ($n = 2$), and pancreatic cancers ($n = 2$).

3.2. Initial presentation

Twenty-three patients (24.7%) had nosocomial bacteremia. Fifty-one patients (54.8%) had polymicrobial bacteremia with the following organisms isolated from concurrent blood cultures: *Escherichia coli* ($n = 21$ patients), *Klebsiella pneumoniae* ($n = 11$), coagulase-negative staphylococci ($n = 8$), anaerobic flora ($n = 5$), and others ($n = 19$).

The mean Pitt bacteremia and Charlson WIC scores were 2.4 and 3.6, respectively. Most patients presented initially with systemic inflammation such as fever, leukocytosis, anemia, and thrombocytopenia. Abdominal pain was noted most often (42 patients, 45.2%), followed by change of consciousness and shock.

3.3. Sources of bacteremia, therapy, and outcomes

Intra-abdominal infection (IAI) was the most common source of bacteremia (49/93, 52.7%), and most patients in this group underwent either surgical intervention (12/49, 24.5%) or palliative drainage (14/49, 28.6%) during the treatment period. Of the IAI patients, 32 (65.3%) had polymicrobial bacteremia and their 30-day mortality was 22.4% (11/49). The most common comorbidities were malignancy (22/49, 44.9%), liver cirrhosis (12/49, 24.5%), and gall stones (6/49, 12.2%).

Twenty-three patients (24.7%) had primary *C. perfringens* bacteremia. Of these, 10 had malignancies, including hepatocellular carcinoma ($n = 4$) and other GI sites ($n = 4$). Six patients (26.1%) died in this group.

The third most common identified source was the lower respiratory tract. Eighteen patients (19.3%) had lower respiratory tract infections (pneumonia, $n = 17$; empyema, $n = 1$) with a high rate of respiratory failure (10/18, 55.6%) and 30-day mortality (8/18, 44.4%).

Of the 93 studied patients, 59 (63.4%) received adequate antimicrobial treatment and 30 (32.3%) had adjunctive surgery or drainage. Among the patients with adequate antimicrobial treatment, imipenem/cilastatin was used for four cases, flomoxef for one, piperacillin/tazobactam for one, clindamycin for one, a combination of two or more antibiotics containing metronidazole for 38, a combination containing clindamycin for nine, and a combination containing penicillin derivatives for five. The mean length of hospitalization was 23.3 days. The 30-day and attributed mortalities were 26.9% (25/93) and 8.6% (8/93), respectively.

3.4. Antimicrobial susceptibility testing

Most *C. perfringens* blood isolates were susceptible to the antibiotics tested (Table 1); resistance was observed in only seven isolates, primarily to penicillin ($n = 4$ patients) and clindamycin ($n = 3$). Of the seven drug-resistant isolates, five (71.4%) were community-acquired.

3.5. Risk factors for 30-day mortality

The univariate analysis of the risk factors for 30-day mortality is shown in Table 2. There were no significant differences in demographics, comorbidities, polymicrobial bacteremia, sources of bacteremia, and therapies between those who survived and those who died. Compared to the patients who survived, those who died had a higher rate of nosocomial infections (56.0% vs. 13.2%, $p < 0.001$), anemia (80.0% vs. 54.4%, $p = 0.025$), and shock at presentation (28.0% vs. 11.8%, $p = 0.003$). The deceased also had higher Pitt bacteremia scores (4.4 ± 3.91 vs. 1.6 ± 2.13, $p = 0.009$) and Charlson WIC (5.0 ± 2.41 vs. 3.0 ± 2.53, $p = 0.001$) than those who survived. In addition, those who survived had a higher rate of

Table 2
Univariate analysis of the risk factors for 30-day mortality

Variables	Survived[a] (n = 68)	Died[a] (n = 25)	OR (95% CI)	p-Value
Demographics				
Male gender	40 (58.8%)	14 (56.0%)	0.891 (0.353–2.248)	0.807
Age, years	71.1 ± 13.47	69.5 ± 12.30		0.607
Comorbidities				
Renal insufficiency	30 (44.1%)	16 (64.0%)	2.252 (0.874–5.803)	0.089
Malignancy	25 (36.8%)	14 (56.0%)	2.189 (0.863–5.553)	0.096
Hypertension	17 (25.0%)	7 (28.0%)	1.167 (0.416–3.272)	0.769
Diabetes mellitus	13 (19.1%)	8 (32.0%)	1.991 (0.707–5.605)	0.188
Liver cirrhosis	10 (14.7%)	6 (24.0%)	1.832 (0.588–5.710)	0.355
Cerebral vascular accident	9 (13.2%)	2 (8.0%)	0.570 (0.114–2.841)	0.721
Heart failure	7 (10.3%)	3 (12.0%)	1.188 (0.282–5.004)	0.814
Use of immunosuppressants	5 (7.4%)	5 (20.0%)	3.150 (0.827–12.003)	0.126
Gall stones	6 (8.8%)	0 (0)	N/A	0.186
Bowel obstruction	2 (2.9%)	0 (0)	N/A	1
Recent admission	11 (16.2%)	8 (32.0%)	2.439 (0.845–7.036)	0.093
Recent surgery	6 (8.8%)	5 (20.0%)	2.583 (0.712–9.379)	0.139
Initial presentations				
Nosocomial infection	9 (13.2%)	14 (56.0%)	8.343 (2.902–23.991)	<0.001
Polymicrobial bacteremia	39 (57.4%)	12 (48.0%)	0.686 (0.274–1.723)	0.422
Pitt bacteremia score	1.6 ± 2.13	4.4 ± 3.91		0.009
Charlson WIC	3.0 ± 2.53	5.0 ± 2.41		0.001
Leukocytosis	38 (55.9%)	14 (56.0%)	1.005 (0.399–2.530)	0.992
Leukopenia	5 (7.4%)	5 (20.0%)	3.150 (0.827–12.003)	0.081
Neutropenia	1 (1.5%)	2 (8.0%)	5.826 (0.504–67.295)	0.114
Anemia	37 (54.4%)	20 (80.0%)	3.35 (1.127–9.968)	0.025
Thrombocytopenia	25 (36.8%)	13 (52.0%)	1.863 (0.738–4.707)	0.185
Abnormal liver function	35 (51.5%)	15 (60.0%)	1.414 (0.558–3.587)	0.465
Liver dysfunction	27 (39.7%)	12 (48.0%)	1.402 (0.557–3.527)	0.472
Fever	36 (52.9%)	16 (64.0%)	1.580 (0.614–4.067)	0.341
Abdominal pain	36 (52.9%)	6 (24.0%)	0.281 (0.100–0.789)	0.013
Change of consciousness	8 (11.8%)	7 (28.0%)	2.917 (0.930–9.147)	0.059
Shock at presentation	4 (5.9%)	7 (28.0%)	6.222 (1.637–23.648)	0.003
Weakness	4 (5.9%)	3 (12.0%)	2.182 (0.452–10.523)	0.381
Hypothermia	3 (4.4%)	4 (16.0%)	4.127 (0.854–19.951)	0.081
Gas formation	3 (4.4%)	3 (12.0%)	2.955 (0.555–15.722)	0.338
Source of bacteremia				
Intra-abdominal	38 (55.9%)	11 (44.0%)	0.620 (0.246–1.562)	0.39
Unknown primary	17 (25.0%)	6 (24.0%)	0.947 (0.325–2.760)	0.921
Lower respiratory tract	10 (14.7%)	8 (32.0)	2.729 (0.931–8.001)	0.061
Upper respiratory tract	1 (1.5%)	0 (0)	N/A	1
Skin, soft tissue, and bone	1 (1.5%)	0 (0)	N/A	1
Urinary tract	1 (1.5%)	0 (0)	N/A	1
Therapy				
Adequate antibiotic use	44 (64.7%)	15 (60.0%)	0.818 (0.319–2.099)	0.676
Adjunctive therapy	23 (33.8%)	7 (28.0%)	0.761 (0.278–2.083)	0.594
Stay in ICU	19 (27.9%)	12 (48.0%)	2.381 (0.924–6.135)	0.069
Length of hospital stay, days	25.6 ± 25.27	17.0 ± 12.18		0.03

OR, odds ratio; CI, confidence interval; N/A, not available; WIC, weighted index of comorbidity; ICU, intensive care unit.
[a] Results are n (%), or mean ± standard deviation.

abdominal pain (52.9% vs. 24.0%, p = 0.013) and longer hospitalization (25.6 ± 25.27 vs. 17.0 ± 12.18, p = 0.030) than those who died.

All variables with $p < 0.1$ were included in the multivariate analysis; the independent risk factors were as follows: nosocomial infections (OR 19.378, 95% CI 2.12–176.99; p = 0.009), Charlson WIC (OR 1.666, 95% CI 1.06–2.62; p = 0.027), length of hospitalization (OR 0.904, 95% CI 0.83–0.98; p = 0.018), and stay in the ICU (OR 9.923, 95% CI 1.06–92.70; p = 0.044) (Table 3).

3.6. Univariate analysis of nosocomial and community-acquired *C. perfringens* bacteremia

Of the 23 patients with nosocomial *C. perfringens* bacteremia (Table 4), the mean hospital stay before the onset of bacteremia was 19.4 days (range 2–50 days). No significant differences existed between the patients with nosocomial and community-acquired bacteremia with regard to age, major comorbidities, therapy, and length of hospitalization after bacteremia. Compared to patients with community-acquired bacteremia, patients with nosocomial bacteremia had a significantly higher rate of male gender (78.3% vs. 51.4%, p = 0.024), immunosuppressant use (26.1% vs. 5.7%, p = 0.006), fever (78.3% vs. 51.4%, p = 0.020), leukocytosis (39.1% vs. 61.4%, p = 0.060), and 30-day mortality (60.9% vs. 15.7%, p = 0.020). Also, patients with nosocomial bacteremia had a lower rate of abdominal pain than patients with community-acquired bacteremia (17.4% vs. 54.3%, p = 0.002). Patients with nosocomial bacteremia had higher Pitt bacteremia scores (3.5 vs. 2.0, p = 0.031)

Table 3
Multivariate analysis of the risk factors for 30-day mortality[a]

Variable	OR (95% CI)	p-Value
Nosocomial infection	19.378 (2.12–176.99)	0.009
Length of hospital stay	0.904 (0.83–0.98)	0.018
Charlson WIC	1.666 (1.06–2.62)	0.027
ICU stay	9.923 (1.06–92.70)	0.044

OR, odds ratio; CI, confidence interval; WIC, weighted index of comorbidity; ICU, intensive care unit.
[a] All variables included in the final multivariable model are displayed above.

Table 4
Univariate analysis for the comparison between nosocomial and community-acquired *Clostridium perfringens* bacteremia

Variables[a]	Nosocomial[b] ($n=23$)	Community-acquired[b] ($n=70$)	OR (95% CI)	p-Value
Demographics				
Male gender	18 (78.3%)	36 (51.4%)	3.40 (0.14–10.17)	0.024
Age, years	67.4 ± 11.64	71.8 ± 13.47		0.166
Comorbidities				
Renal insufficiency	12 (52.2%)	34 (48.6%)	1.16 (0.45–2.97)	0.764
Malignancy	13 (56.5%)	26 (37.1%)	2.20 (0.85–5.73)	0.102
Use of immunosuppressants	6 (26.1)	4 (5.7)	5.82 (1.48–22.98)	0.006
Initial presentations				
Pitt bacteremia score	3.5 ± 3.41	2.0 ± 2.75		0.031
Charlson WIC	4.8 ± 2.31	3.1 ± 2.60		0.007
Fever	18 (78.3%)	36 (51.4%)	3.40 (1.14–10.17)	0.02
Leukocytosis	9 (39.1%)	43 (61.4%)	0.40 (0.15–1.06)	0.06
Abdominal pain	4 (17.4%)	38 (54.3%)	0.18 (0.06–0.56)	0.002
Sources of bacteremia				
Intra-abdominal	8 (34.8%)	41 (58.6%)	0.38 (0.14–1.01)	0.047
Unknown primary	9 (39.1%)	14 (20.0%)	2.57 (0.93–7.14)	0.065
Lower respiratory tract	6 (26.1%)	12 (17.1%)	1.71 (0.56–5.22)	0.370
Therapy				
Adequate antibiotic use	11 (47.8%)	48 (68.6%)	0.42 (0.16–1.10)	0.073
Adjunctive therapy	4 (17.4%)	26 (37.1%)	0.36 (0.11–1.16)	0.079
Outcomes				
30-day mortality	14 (60.9%)	11 (15.7%)	8.34 (2.90–23.99)	<0.001
LOS after bacteremia, days	15.2 ± 11.38	15.2 ± 24.27		0.068

OR, odds ratio; CI, confidence interval; WIC, weighted index of comorbidity; LOS, length of hospital stay.
[a] Only significant ($p<0.05$) and selected non-significant variables are shown.
[b] Results are n (%), or mean ± standard deviation.

and Charlson WIC (4.8 vs. 3.1, $p=0.007$) than patients with community-acquired bacteremia.

4. Discussion

To the best of our knowledge, this study represents the largest assessment of the incidence, risk factors, and outcomes of patients with *C. perfringens* bacteremia in a hospital-based population. Several studies on clostridial infections have provided potentially valuable insight and clinical experience, but they have not distinguished the characteristic disease types caused by the individual pathogen from other undefined *Clostridium* species.[11,13,14,22] Those studies indicated that many clostridial blood isolates may have no clinical significance.[16,23] Several recent studies have demonstrated that *Clostridium* species are usually pathogenic under certain conditions and that failure to institute early, appropriate antimicrobial therapy may be associated with a poor outcome.[13,22,24] Our study used a strict definition for *C. perfringens* bacteremia, and 72.7% of the clinical blood isolates were clinically significant. Physicians should be alert to elderly patients with abdominal pain, septic symptoms, and polymicrobial infections, which may be suggestive of *C. perfringens* bacteremia.

The 30-day mortality was 26.9%, nearly identical to that found in a previous study by Fujita et al.[5] That study included 18 cases of *C. perfringens* bacteremia; the case population was elderly, and the 30-day mortality rate was 27%. The only medical characteristic related to mortality was shock. Most of our patients received adequate antimicrobial therapy initially, however the treatment did not correlate to the prognosis. Patients with nosocomial infections or poor health status, such as those with a high Charlson WIC or stay in the ICU, had a higher mortality rate.

In our study, extreme age and multiple comorbidities, such as renal insufficiency and malignancy, significantly increased the risk of acquiring *C. perfringens* bacteremia. The increased risk may be due to the increased number of comorbid illnesses in elderly people and perhaps more age-related colonization of *Clostridium* species in the intestine.[22] One study reported that hemodialysis patients had an increased risk for developing Clostridium bacteremia compared to the general population.[22,25] Frequent vascular access and the higher incidence of concurrent comorbid illness in that population may increase the risk of clostridial infections.[25]

Cancer and immunosuppression are consistently reported as the main comorbidities in patients infected with *C. perfringens*.[10,26] Similarly, 39 patients (41.9%) in our study had malignancies, and of note, hepatocellular carcinoma and cholangiocarcinoma predominated. This differentiates our study from the previous study.[26] Malignancy itself is a potential factor that can destroy the mucosal barrier and thereby increase the potential for bloodstream infections.[14,27] Furthermore, the GI mucosal injury may be caused by cytotoxic drugs, radiation, chemotherapy, or embolization.[10] Besides invasive infections through the GI mucosa, any condition that causes respiratory tract tunnel formation, lumen obstruction, and swallowing difficulties may result in aspiration pneumonia of the oropharyngeal or GI flora.

Nosocomial *C. perfringens* bacteremia was not rare in our patients (23/93, 24.7%) and caused a mortality rate of up to 60.9%. Further, nosocomial infection was a significant predictor of 30-day mortality independent of other parameters. At the time of bacteremia onset, patients with nosocomial *C. perfringens* bacteremia may have several underlying diseases and poor anaerobic flora coverage. Thus, the prognosis of this population is relatively poor. More than a half of patients with community-acquired *C. perfringens* bacteremia had IAI, and this finding should alert physicians to give broad-spectrum coverage for anaerobes and administer appropriate adjunctive therapies to destroy the residential environments of *C. perfringens*.

The Pitt bacteremia score has been used to predict the mortality of bacteremia more commonly than the APACHE II scoring system and the Charlson WIC, because of its higher sensitivity and specificity for bacteremia caused by certain bacterial strains, including *Staphylococcus aureus*, extended-spectrum beta-lactamase-producing *E. coli*, *Pseudomonas aeruginosa*, and *Fusobacterium nucleatum*.[21,27] In our study, the Pitt bacteremia score was not an effective predictor for the prognosis of *C. perfringens* bacteremia. Instead, the Charlson WIC was more effective for predicting the

prognosis as it reflected the multiple comorbidities in our patient population.

Compared to the 14% of clindamycin resistance (overall) for *C. perfringens* isolates in Canada,[22] the isolates in our study exhibited a high in vitro susceptibility to penicillin, ampicillin/sulbactam, piperacillin, metronidazole, and clindamycin (all >90%).

This study has several limitations. First, we only included hospitalized patients and not outpatients referred from or transferred to other hospitals. Patients with incomplete medical records and those who were lost to follow-up after discharge were also excluded. Second, the antibiotic regimens varied among individual cases, hence it was difficult to evaluate the efficacy and draw conclusions on the optimal therapeutic strategies for such a critical infection.

In summary, *C. perfringens* bacteremia, although relatively uncommon, is associated with a significant disease burden, especially intra-abdominal infections and pneumonia. Patients with multiple comorbid illnesses, especially renal insufficiency and malignancy, are at the highest risk for acquiring this type of infection. Nosocomial bacteremia was a significant mortality predictor independent of other parameters of disease severity. It is important that this critical infection is recognized earlier and that appropriate antibiotic treatment with surgical debridement or drainage is initiated as soon as possible.

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